Remarks

I. Status

Claims 28-36 are pending. All claims stand rejected as indefinite pursuant to 35 USC § 112, second paragraph, and as anticipated by certain cited references pursuant to 35 USC § 102(b).

Applicants have amended the claims to more clearly describe their invention. The claims have thus been amended to clarify that the cross-over proteins are formed through the ligation of an N-terminal peptide segments with an C-terminal peptide segment to yield a cross-over protein having a C-terminal and an N-terminal, and that the amino acid sequences of such segments comprise functional domains of different proteins. Support for this recitation can be found throughout the specification (see, for example, page 29, lines 15-18. No new matter has been introduced by these amendments.

II. Information Disclosure Statement

The form PTO-1449 accompanying the Official Action indicates that certain references cited and provided by Applicants could not be located in the Examiner's files. Applicants have enclosed submit duplicate copies of these documents, and request that they be considered and made of record in the prosecution of the present application. The Examiner is requested to initial the enclosed Form 1449 to indicate consideration of these documents. No new fee is believed due to consider such references and to make them of record in the present application. However, if in the opinion of the Commissioner, a fee is required for such action, Applicants authorize the fee to be charged to Deposit Account 50-0548.

III. The Objection to the Abstract of the Invention

The Examiner has objected to the phraseology of the Abstract of the Invention. Applicants have accordingly amended the specification, and respectfully submit that such amendment fully respond to the Examiner's concerns. Applicants accordingly submit that the Examiner's objections to the Abstract of the Invention may now be properly withdrawn.

IV. The Rejection of the Claims as Indefinite Pursuant to 35 USC § 112, Second Paragraph

The Examiner has rejected claims 28-36 as indefinite pursuant 35 USC § 112, second paragraph. Applicants have accordingly amended the claims in order to more clearly describe Applicants' invention. Applicants respectfully submit that such amendments fully respond to the Examiner's concerns. Applicants accordingly submit that the Examiner's rejection of the claims pursuant to 35 USC § 112, second paragraph may now be properly withdrawn.

V. The Rejection of Claims 28-31 pursuant to 35 USC § 102(b) as Anticipated by Canne *et al.* (J. Am. Soc.), Dawson *et al.*, Clark-Lewis *et al.* (Biochemistry), Clark-Lewis *et al.* (J. Biol. Chem.); Gaertner *et al.* or Schnölzer *et al.* (Science)

The Examiner has rejected claims 28-31 as anticipated pursuant to 35 USC § 102(b) in light of Canne *et al.* (J. Am. Soc.), Dawson *et al.*, Clark-Lewis *et al.* (Biochemistry), Clark-Lewis *et al.* (J. Biol. Chem.); Gaertner *et al.* or Schnölzer *et al.* (Science), each applied singly. Applicants respectfully traverse the Examiner's rejection and request reconsideration in light of the amended claims.

A. The Rejection in Light of Canne *et al.* (J. Am. Soc.)

The claims of the present invention have been amended to more clearly describe the nature of the ligation reaction as involving N-terminal and C-terminal peptide

segments derived from the amino acid sequences of different proteins, such that a cross-over protein having an N-terminus and a C-terminus is formed. Applicants respectfully submit that such invention is neither disclosed nor suggested by the cited Canne *et al.* reference (J. Am. Soc.). In this regard, Applicants respectfully draw the Examiner's attention to the fact that the cMyc-Max molecule described by Canne *et al.* is formed via an ***C-terminal to C-terminal ligation*** of cMyc and Max peptide domains (see page 2999, first sentence of paragraph bridging left and right columns), and that the resulting ligation product thus possesses ***two N-termini and no C-terminus***. Accordingly, Applicants respectfully submit the Examiner's rejection of the claims in light of the Canne *et al.* reference may be properly withdrawn.

B. The Rejections in Light of Dawson *et al.*, Gaertner *et al.* and Schnölzer et al. (Science)

Applicants respectfully submit that the presently claimed invention is not anticipated in light of Dawson *et al.*, Gaertner *et al.*, or Schnölzer *et al.* (Science).

Dawson *et al.* describes the use chemical ligation to join together peptide fragments of the same protein. As the Examiner will note, the reference fails to teach or suggest the invention of producing cross-over proteins that are composed of peptide segments from ***different*** proteins. In this regard, Applicants respectfully draw the Examiner's attention to the experimental methods outlined at page 777 of the Dawson *et al.* document, which clarify that the document discloses the ligation of peptide sub-segments of the ***same*** protein (IL-8).

Gaertner *et al.* and Schnölzer *et al.* (Science) likewise describe the use chemical ligation to join together peptide fragments of the ***same*** protein. In this regard, Applicants respectfully draw the Examiner's attention to the experimental methods outlined at page 334 and 337 of the Gaertner *et al.* document, which clarify the document is concerned with the religation of two fragments obtained by enzymatic cleavage of G-CSF. Similarly, Schnölzer *et al.* (Science) concerns reacting the amino-terminal half of HIV-1

PR with the corresponding unprotected carboxyl-terminal half to yield the full-length molecule (see page 222,first full paragraph of right column).

Applicants submit that the presently claimed invention is thus not anticipated by Dawson *et al.*, Gaertner *et al.* or Schnölzer *et al.* (Science). Accordingly, Applicants respectfully submit that the Examiner's rejection of claims 28-31 in light of these references may be properly withdrawn.

C. The Rejection in Light of Clark-Lewis *et al.* (Biochemistry)

Applicants respectfully submit that the presently claimed invention is not anticipated in light of Clark-Lewis *et al.* (Biochemistry). The Clark-Lewis *et al.* (Biochemistry) reference describes the use of solid phase amino acid synthetic chemistry to produce IL-8 analogues and variants. Applicants respectfully submit to the Examiner appears to have inadvertently misapprehended the teachings of a reference. Specifically, contrary to the apparent conclusion of the Examiner, the reference does not teach the ligation of two oligopeptides, one of which comprises sequences of IL-8 and one of which comprises sequences of (NAP-1) neutrophil activating peptide-1. As the Examiner will note, the reference discloses that "IL-8" and "NAP-1" ***are one and the same the protein***:

> "The first protein with these activities to be identified was variously termed neutrophil activating factor..., monocyte-derived neutrophil activating peptide..., and monocyte-derived neutrophil chemotactic factor.... More recently, the terms neutrophil activating peptide 1 (NAP-1) and interleukin-8 (IL-8) were proposed.... (page 3128, first two sentences of right column)

Accordingly, the cited Clark-Lewis *et al.* (Biochemistry) document fails to teach or suggest the ligation of peptide segments having the amino acid sequences of different protein molecules. As such, Applicants respectfully submit that the rejection in light of the Clark-Lewis *et al.* (Biochemistry) reference may be properly withdrawn.

D. The Rejection in Light of Clark-Lewis *et al.* (J. Biol. Chem.)

Applicants respectfully submit that the presently claimed invention is additionally not anticipated in light of Clark-Lewis *et al.* (J. Biol. Chem.). The Clark-Lewis *et al.* (J. Biol. Chem.) reference describes the use of solid phase amino acid synthetic chemistry to produce IL-8 analogues and variants. As the Examiner will note, the reference fails to teach or suggest the approach of producing such variants through the ***ligation of at least two peptide segments*** as recited in Applicant's claims. In this regard, Applicants draw the Examiner's attention to the experimental methods outlined at page 16076 of the document.

Applicants respectfully submit that the presently claimed invention is thus not anticipated by the Clark-Lewis *et al.* (J. Biol. Chem.) document. Accordingly, Applicants submit that the Examiner's rejection in light of Clark-Lewis *et al.* (J. Biol. Chem.) may be properly withdrawn.

VI. The Rejection of Claims 32-34 pursuant to 35 USC § 102(b) as Anticipated by Cwirla *et al*

The Examiner has rejected claims 32-34 as anticipated pursuant to 35 USC § 102(b) in light of Cwirla *et al.* Applicants respectfully traverse the Examiner's rejection and request reconsideration in light of the amended claims.

The cited Cwirla *et al.* document concerns the use recombinant DNA technology to produce a diverse oligonucleotide library that can then be inserted into the gene III of filamentous phage to create infective "fusion phage" that display foreign peptides on their surface (see Cwirla et al., page 6378). As the Examiner will appreciate, such a method of producing peptide and protein molecules does not involve the act of ***ligating*** (whether under chemoselective reaction conditions or other conditions) a plurality of unique N-terminal ***peptide*** segments with a plurality of unique C-terminal ***peptide*** segments. Applicants respectfully submit that those of ordinary skill in the art would not have

understood the recombinant DNA teaching of Cwirla *et al.* to disclose or suggest the chemical ligation of ***peptide*** segments. Accordingly, Applicants respectfully submit that the cited Cwirla *et al.* reference fails to anticipate claims 32-34, and that the rejection of such claims in light of the reference may be properly withdrawn.

VII. The Rejection of Claims 28-36 pursuant to 35 USC § 102(b) as Anticipated by Stricht *et al.* or Zuckerman *et al*

The Examiner has rejected claims 28-36 as anticipated pursuant to 35 USC § 102(b) in light of Stricht *et al.* or Zuckerman *et al.* Applicants respectfully traverse the Examiner's rejection and request reconsideration in light of the amended claims.

A. The Rejection in Light of Stricht *et al.*

Applicants respectfully submit that the cited Stricht *et al.* reference fails to anticipate any of the claims of the present invention. The Stricht *et al.* reference is directed to the use of recombinant DNA technology to form a chimeric gene whose encoded protein contains an N-terminal portion of IL 8 and a C-terminal portion of Melanoma Growth Stimulatory Activity (MGSA) protein. In this regard, Applicants respectfully draw the Examiner's attention to paragraph entitled "Generation of the Chi1 Mutant" on page 27 of the reference. Therein, Stricht *et al.* disclose that the Chi1 mutant was derived from an expression construct containing a synthetic gene encoding the mature 72-amino acid IL-8. As such, Applicants respectfully submit that the reference neither discloses the production of a "cross-over protein library" nor the formation of *any* protein through the act of ***ligating under chemoselective reaction conditions a plurality of unique N-terminal peptide segments and a plurality of unique C-terminal peptide segments*** as recited in the claims. Applicants respectfully submit that those of ordinary skill in the art would not have understood the recombinant DNA teaching of Stricht *et al.* to disclose or suggest the chemical ligation of peptide segments being claimed by Applicants. Accordingly, Applicants respectfully submit that the cited Stricht *et al.*

reference fails to anticipate claims 28-36, and that the rejection of such claims in light of the reference should be withdrawn.

B. The Rejection in Light of Zuckerman *et al.*

Applicants respectfully submit that the cited Zuckerman *et al.* reference fails to anticipate any of the claims of the present invention. The Zuckerman *et al.* reference is directed to the production of dimer and trimer *N*-substituted glycine "peptoids."

As disclosed by the reference, such "peptoids" were formed through the derivitization of preformed amines, and not through the ligation of at least one N-terminal peptide segment comprising a *functional protein module derived from a first parent protein*, and at least one C-terminal peptide segment co*mprising a functional protein module derived from a second parent protein*, as recited by the present claims.

Accordingly, Applicants submit that the Zuckerman *et al.* reference fails to anticipate the present claims at least because the disclosed "peptoids":

1. are *not* produced through the ligation of *peptides*;

2. do *not* comprise at least two *peptide segments* each of which comprises a *functional protein module* of a parent protein; and

3. are *not* composed of an amino acid sequence that was derived from either a first or a second *parent protein*.

Accordingly, Applicants respectfully submit that the rejection of claims 28-36 in light of the cited Zuckerman *et al.* reference fails may be properly withdrawn.

VIII. The Rejection of Claims 28-31 pursuant to 35 USC § 102(b) as Anticipated by Wilken

The Examiner has rejected claims 28-31 pursuant to 35 USC § 102(b) as anticipated by Wilken (Document D56). Applicants respectfully draw the Examiner's attention to the September 4, 1997 publication date of the document. Applicants submit that the present application claims a right of priority pursuant to 35 U.S.C. § 119(e) to Provisional U.S. Patent Application Serial No. 60/057,620, which was filed on September 4, 1997. Accordingly, the Wilken (Document D56) reference is not available as prior art to the present application. The rejection of claims 28-31 in light of the Wilken (Document D56) reference should therefore be withdrawn.

VIII. The Provisional Non-Statutory Double Patenting Rejections

The Examiner has provisionally rejected claims 28-31 under the judicially created doctrine of obviousness-type double patenting in light of claims 1-6 of co-pending Application Serial No. 08/945,997 or over claims of co-pending Application Serial No. 09/097,094.[1] Applicants respectfully traverse the rejection and request reconsideration.

As clarified by the Court of Appeals for the Federal Circuit, in assessing the propriety of a double-patenting rejection, one looks to the claims of the two applications rather than to their disclosures. *Panduit Corp. v. Dennison Mfg. Co.*, 227 USPQ 337 (Fed. Cir. 1985). Applicants respectfully submit that an obviousness-tight double patenting rejection is inappropriate in the present circumstance since the present application and Application Serial No. 08/945,997 do not claim the same or similar inventions and hence do not reflect an improper timewise extension of the right to exclude. In this regard, Applicants' amended claim 28 reads as follows:

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[1] The Official Action contains a typographical error in the identification of this patent application. Applicants contacted the Examiner on November 9, 2000, to clarify the correct serial number of the application involved in the Examiner's rejection, and were advised that the correct serial number was 09/097,094. Applicants greatly appreciate the assistance of the Examiner.

28. [Amended] A method of producing a cross-over protein that contains at least one peptide segment from one parent protein and at least one peptide segment from a second parent protein, said method comprising: ligating under chemoselective chemical ligation conditions (i) at least one N-terminal peptide segment comprising a functional protein module derived from said first parent protein, and (ii) at least one C-terminal peptide segment comprising a functional protein module derived from said second parent protein having an amino acid sequence that is different from said first parent protein, wherein said N-terminal peptide segment and said C-terminal peptide segment comprise compatible reactive groups capable of chemoselective chemical ligation to one another, whereby a covalent bond is formed between said N-terminal peptide segment and said C-terminal peptide segment so as to produce a chemical ligation product comprising a cross-over protein having a C-terminus and an N-terminus.

Claim 1 of the '997 Application reads as follows:

1. A method for ligating a first oligopeptide with a second oligopeptide end to end for producing an oligopeptide product, the method comprising the following steps:

Step A: admixing of the first and second oligopeptides in a reaction solution including a catalytic thiol, the first oligopeptide including a C-terminal thioester, the second oligopeptide including an N-terminal cysteine having an unoxidized sulfhydryl side chain; then

Step B: condensing the unoxidized sulfhydryl side chain of the N-terminal cysteine with the C-terminal thioester for producing an intermediate oligopeptide linking the first and second oligopeptides with a β-aminothioester bond; and then

Step C: rearranging the β-aminothioester bond of the intermediate oligopeptide of said Step B for producing the oligopeptide product linking the first and second oligopeptides with an amide bond.

As is apparent, from a comparison of claim 28 of the present application and claim 1 of the '997 application, the inventions of these applications are drawn to substantially dissimilar and clearly patentably distinct inventions. The claims of these inventions possess very different attributes:

Attribute	
Claim 28 of the Present Invention	**Claim 1 of the '997 Application**
1. Sequence of each oligopeptide must be derived from two different proteins	1. Sequence of each oligopeptide need ***not*** be derived from two different proteins
2. Each peptide must comprise a functional protein module	2. Each peptide need ***not*** comprise a functional protein module
3. No requirement that one oligopeptide possess a C-terminal thioester	3. One oligopeptide must possess a C-terminal thioester
4. No requirement that one oligopeptide possess a C-terminal thioester	4. One oligopeptide must possess an N-terminal cysteine
5. No requirement that any peptide have an unoxidized sulfhydryl side chain	5. The N-terminal cysteine must have an unoxidized sulfhydryl side chain
6. No requirement for the formation of a β-aminothioester bond between the two peptides;	6. Requires the formation of a β-aminothioester bond between the two peptides;
7. No requirement for the presence of a catalytic thiol	7. Requires the presence of a catalytic thiol
8. No requirement for the linking of the peptides via an amide bond	8. Requires the linking of the peptides via an amide bond

Applicants respectfully submit that an obviousness-tight double patenting rejection is likewise inappropriate since the present application and Application

Serial No. 09/097,094 do not claim the same or similar inventions and hence do not reflect an improper timewise extension of the right to exclude.

Claim 1 of the '094 application reads as follows:

1. A method of producing an assembled peptide in aqueous solution and a solid phase comprising:
   a) binding an unprotected first peptide segment to a solid phase via a linker, wherein said unprotected first peptide segment comprises an N-terminus and a thioester of the formula -COSR at its C-terminus, wherein said linker comprises a cleavable moiety and said unprotected first peptide segment is bound to said linker at said N-terminus;
   b) ligating a second unprotected peptide segment to said first peptide segment bound to said solid phase, wherein said second peptide segment comprises a cysteine and its N-terminus and a thioacid and its C-terminus, and wherein said N-terminal cysteine of said second peptide segment is capable of selectively ligating to said C-terminus of said solid phase-bound first peptide segment to form a solid phase-bound peptide comprising a thioacid at its C-terminus;
   c) converting said C-terminal thioacid of said solid phase-bound peptide to an activated thioester of the formula -COSR,
   d) repeating steps to b) and c) with a third unprotected peptide segment; and
   e) optionally repeating steps to b) and c) with additional unprotected peptide segments.

As is apparent, from a comparison of claim 28 of the present application and claim 1 of the '094 application, the inventions of these applications are likewise drawn to substantially dissimilar and clearly patentably distinct inventions that possess very different attributes:

Attribute	
Claim 28 of the Present Invention	**Claim 1 of the '094 Application**
1. Sequence of each oligopeptide must be derived from two different proteins	1. Sequence of each oligopeptide need ***not*** be derived from two different proteins
2. Each peptide must comprise a functional protein module	2. Each peptide need ***not*** comprise a functional protein module
3. No requirement that one oligopeptide possess a C-terminal thioester	3. One oligopeptide must possess a C-terminal thioester
4. No requirement that one oligopeptide possess a C-terminal thioester	4. One oligopeptide must possess an N-terminal cysteine
5. No requirement that any peptide be bound to a solid phase	5. At least one peptide must be bound to a solid phase before and after ligation
6. No requirement for a cleavable or uncleavable linker	6. The peptide that is bound to a solid support must be bound through a cleavable linker
7. No requirement that the N-terminus of the ligated peptide be bound to a solid phase	7. The N-terminus of the ligated peptide is bound to a solid phase
8. No requirement for the linking of the peptides via an amide bond	8. Requires the linking of the peptides via an amide bond

Applicants respectfully submit that in light of such numerous and distinct claim limitation differences, the issuance of both the '094 application and the claims of the present application would not serve to improperly extend the "right to exclude." For example, the method to the present application could be conducted using any of oxime forming chemical ligation, thioester forming ligation, thioether forming ligation, hydrazone forming ligation, thiazolidine forming ligation, and oxazolidine forming ligation, without in any way extending the "right to exclude" provided by the '094 application, since the claims of that application concern the use of native chemical ligation. Conversely, the method of claim 1 of the '094 application could be practiced using peptide segments that did not comprise functional protein modules of pre-existing

proteins without an anyway extending the "right to exclude" that would be provided by the present application upon its issuance. Applicants respectfully submit that the presently pending claims define a patentable distinct invention over the invention of the claims of the '094 application. Accordingly, it is submitted that the non-statutory obviousness-type double patenting rejections in light of the '997 and '094 applications may be properly withdrawn.

IX. The Provisional Obviousness Rejection Pursuant to 35 U.S.C. §102(e)/103(a)

The Examiner has provisionally rejected claims 28-31 as obvious pursuant to 35 USC §103(a) in light of co-pending Applications Serial Nos. 08/945,997 or 09/097,094. Applicants respectfully traverse the rejection and request reconsideration.

For the same reasons as discussed above, the present claims are not obvious in light of the disclosures of Applications Serial Nos. 08/945,997 and 09/097,094. The '997 application discloses the use of native chemical ligation to ligate two peptides provided that one peptide contains an N-terminal cysteine having an unoxidized sulfhydryl side chain, and the other peptide contains a C-terminal thioester group. The '094 application describes the ability to perform native chemical ligation on peptides whose N-termini are bound to solid supports via cleavable linkers.

The present invention involves the ligation of two or more peptides. Native chemical ligation is not required by the present invention. Nor does the present invention require the binding of the N-terminus of one peptide to a solid support. Neither the '997 nor the '094 application can be said to teach or suggest such modifications. Indeed, they expressly teach these requirements. Conversely, the present invention requires that the sequences of the peptides being ligated be derived from *different* protein molecules. Neither the '997 nor the '094 application teaches or suggests such an invention.

Applicants moreover respectfully submit that no art cited by the Examiner teaches the modification of the inventions of the '997 or '094 applications that would be needed to attain the present invention. Accordingly, Applicants respectfully submit that the present claims are not obvious in light of the cited '997 and '094 applications, and that the provisional rejection of the claims on this basis may be properly withdrawn.

Having now fully responded to the issues raised by the Examiner, Applicants respectfully submit that the present application is now in condition for Examination, and earnestly solicit early notice of favorable action. The Examiner is invited to contact the undersigned with respect to any issues regarding this application.

Respectfully Submitted,

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